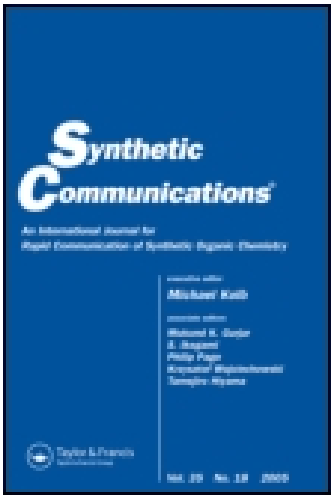


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Thermal Ring Closure Reaction of 4-Methyl-7-(1,1-Disubstituted Propyn-2-Yloxy)Chromen-2-Ones: The Effects of the Substituents at Propargylic Position on Reactivity and Products

Qian Zhang [a] , Ying Chen [a] , Yi Xia [a] , Zhengyu Yang [a] & Peng Xia [a]

[a] Department of Medicinal Chemistry , School of Pharmacy, Fudan University , Shanghai, 200032, China

Published online: 12 Jan 2011.

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 24, pp. 4507–4515, 2004

Thermal Ring Closure Reaction of 4-Methyl-7-(1,1-Disubstituted Propyn-2-Yloxy)Chromen-2-Ones: The Effects of the Substituents at Propargylic Position on Reactivity and Products

Qian Zhang, Ying Chen, Yi Xia, Zhengyu Yang, and Peng Xia*

Department of Medicinal Chemistry, School of Pharmacy, Fudan University, Shanghai, China

ABSTRACT

The thermal ring closure of 4-methyl-7-(1,1-disubstituted propyn-2-yloxy)chromen-2-ones (**1**) with gem-dihydro- or dimethyl-group at the propargylic position was carried out at high temperature such as refluxing in N,N-diethylaniline and resulted in the analogues of 4-methyl-2*H*-pyrano[6,5-*h*]2*H*-chromen-2-one (**2**). As the substituents at the propargylic position became bulkier, this ring closure could occur in much milder conditions such as refluxing in acetone or stirring

*Correspondence: Peng Xia, Department of Medicinal Chemistry, School of Pharmacy, Fudan University, Shanghai 200032, China; Fax: +86-021-54237563; E-mail: pxia@shmu.edu.cn.

DOI: 10.1081/SCC-200043203 0039-7911 (Print); 1532-2432 (Online)

in DMF at 80–90°C. The five-membered products, 4-methyl-furano [2,3-*h*]2*H*-chromen-2-ones (**3**) gradually became the main products.

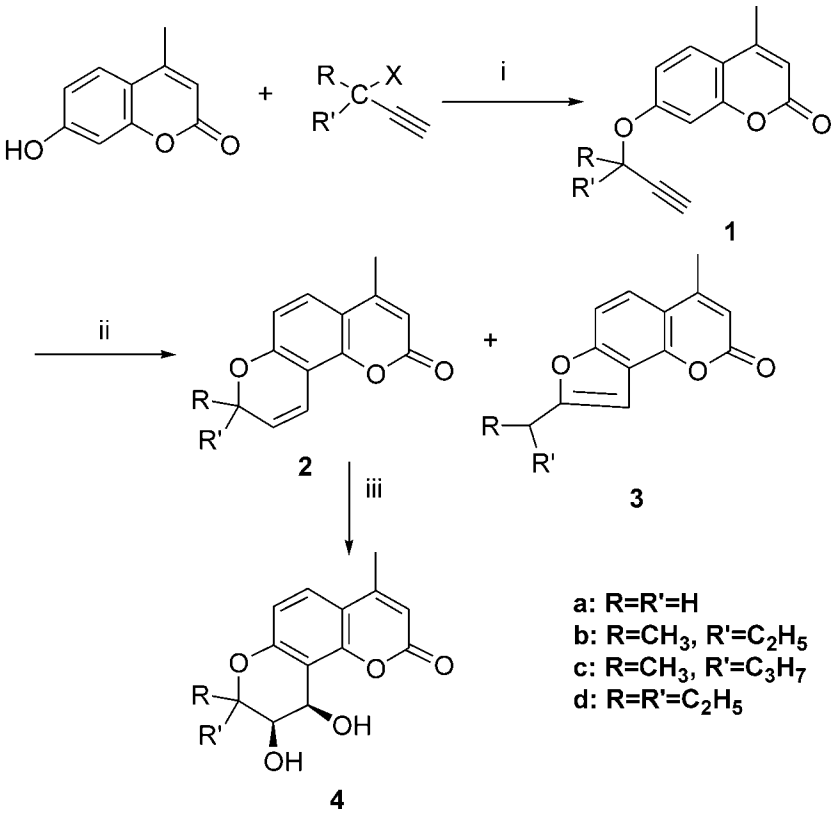
Key Words: Aryl propargylether; 4-methyl-7-(1,1-disubstituted propyn-2-yloxy)chromen-2-ones; Thermal ring closure reaction.

2*H*-Pyrano[6,5-*h*]2*H*-chromen-2-one is an essential core moiety of many potential bioactive compounds, such as the anti-HIV agents suksdorfin[1], inophynone,[2] and calanolide[3], which possess a methyl- or gem-dimethyl-group at the 8-position. The well-known synthetic route to them is via the thermal ring closure reaction of aryl propargyl ether.[4–6] In our previous research aimed at anti-HIV agents, we found that the substituents at the 8-position might have considerable effects on the bioactivities.[7] This prompted us to further synthesize the analogues of 2*H*-pyrano[6,5-*h*]2*H*-chromen-2-one with different substituents at the 8-position via the thermal ring closure of 4-methyl-7-(1,1-disubstituted propyn-2-yloxy)chromen-2-ones. However, the experimental results revealed that the substituents at the propargylic site of the corresponding ethers (**1**) had a great effect on both the reactivity and the ratio of two heterocyclic scaffolds, 4-methyl-2*H*-pyrano[6,5-*h*]2*H*-chromen-2-one (**2**) and 4-methyl-furano[2,3-*h*]2*H*-chromen-2-one (**3**), in products.

As Sch. 1 shows, the reaction of 4-methyl-7-hydroxy-2*H*-chromen-2-one with propargylic bromide (**a**: R=R′=H) gave 4-methyl-7-(2-propynyloxy)2*H*-chromen-2-one (**1a**), which was heated in N,N-diethylaniline to give the normal six-membered ring closure product, 4-methyl-2*H*-pyrano[6,5-h]2*H*-chromen-2-one (**2a**), exclusively. This result was similar to the reported thermal reaction of 7-(1,1-dimethyl propyn-2-yloxy)chromen-2-one.[8]

To our surprise, besides the normal desired propargylic ether product, 7-(1-methyl-1-ethyl-2-propynyloxy)-4-methyl-2*H*-chromen-2-one (**1b**), some further ring closure products, 4,8-dimethyl-8-ethyl-2*H*-pyrano[6,5-*h*]2*H*-chromen-2-one (**2b**) and 4-methyl-8-(1′-methylpropyl)furano[2,3-*h*]2*H*-chromen-2-one (**3b**) were isolated from the reaction of 4-methyl-7-hydroxy-2*H*-chromen-2-one with 3-methyl-3-chloro-1-pentyne (**b**: $R = CH_3$, $R' = C_2H_5$) in the presence of K_2CO_3 and KI by refluxing in acetone.

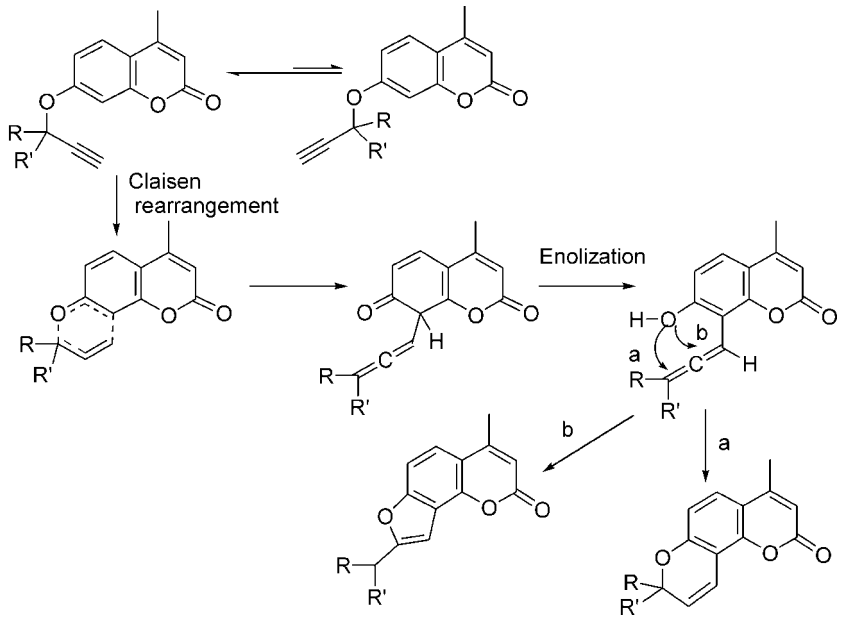
As the substituents at the propargylic position became more bulky, 3-methyl-3-chloro-1-hexyne (**c**: $R = CH_3$, $R' = C_3H_7$) and 3-ethyl-3-chloro-1-pentyne (**d**: $R = R' = C_2H_5$) reacted with 4-methyl-7-hydroxy-2*H*-chromen-2-one to give a mixture of the corresponding ring closure products **2** and **3** exclusively, without the formation of the normal propargylic ethers **1**. The experiment reveals that the initial propargylic ether intermediates with bulkier substituents at the propargylic position could undergo the ring closure under the condition of refluxing in acetone or stirring in DMF at 80–90°C.



Scheme 1. Reaction agents and conditions: 1) K_2CO_3 and KI in refluxing acetone or in DMF at 80–90°C; 2) refluxing in N,N-diethylaniline or refluxing in acetone or stirring in DMF at 80–90°C; 3) AD-mix-α in *n*-BuOH/H_2O (1 : 1) at 0–4°C.

In the previously reported method, this thermal ring closure occurred only at higher temperature by refluxing in various solvents with a high boiling point such as N,N-diethylaniline, N,N-dimethylaniline, diphenyl ether, etc. (195–220°C).[4–6] The easy ring closure of 4-methyl-7-(1,1-bulky disubstituted propyn-2-yloxy)chromen-2-ones at a lower temperature might result from their preferred conformations: the bulkier substituents at the propargylic site force the ethynyl group close to the benzene moiety, thus leading to the occurrence of the Claisen rearrangement at 8-position of 1 (as shown in Sch. 2).

Many efforts were unsuccessful to separate the six-membered ring closure product (**2**) and the five-membered ring closure product (**3**) because



Scheme 2.

of their similar physical properties. Finally, we separated them via further dihydroxylation. The double bond in the pyran ring of 2*H*-pyrano[6,5-*h*]2*H*-chromen-2-ones (**2**) reacted with AD-mix-α to give the 9R,10R-dihydroxy-compounds (**4**), but the double bond in the furan ring of furano[2,3-*h*]2*H*-chromen-2-ones (**3**) did not react, and (**3**) remained in the reaction mixture completely unchanged owing to their aromaticity. In this step, the dihydroxylated compounds of 2*H*-pyrano[6,5-*h*]2*H*-chromen-2-ones (**4b–d**) and unchanged furano[2,3-*h*]2*H*-chromen-2-ones (**3b–d**) could be separated easily. Based on the yield of **4b–d** and **3b–d**, the approximate ratio of **2** and **3** in the last ring closure reaction is listed in Table 1.

Additionally, as shown in Table 1, the bulkiness of the substituents at the propargylic position of 4-methyl-7-(1,1-disubstituted propyn-2-yloxy) chromen-2-ones also affected the ratio of the six-membered and five-membered ring closure products. It demonstrated that the substrates with bulkier substituents were favored to form the five-membered products, furano[2,3-*h*]2*H*-chromen-2-ones (**3**), due to the steric hindrance in the formation of the six-membered ring (path a in Sch. 2).

Table 1. The approximate ratio of *2H*-pyrano[6,5-*h*]2*H*-chromen-2-ones (**2**) and furano[2,3-*h*]2*H*-chromen-2-ones (**3**) in ring closure reaction.

	2*H*-Pyrano[6,5-*h*]2*H*-chromen-2-ones (**2**) (%)	Furano[2,3-*h*]2*H*-chromen-2-ones (**3**) (%)
a: R = R′ = H	100	0
b: R = CH_3, R′ = C_2H_5	80	20
c: R = CH_3, R′ = C_3H_7	55	45
d: R = R′ = C_2H_5	15	85

EXPERIMENTAL

General Synthesis for 1a–b

Excessive propargylic halide was added into a mixture of 4-methyl-7-hydroxycoumarin (4.00 g, 22.70 mmol), K_2CO_3 (40 g, 0.29 mol), and KI (3.77 g, 2.70 mmol) in 200 mL DMF. After stirring at 80–90°C for 7–30 h, the mixture was cooled and filtered. A white solid (**1a–b**) was obtained after removal of the solvent and purified by flash column chromatography (petroleum: $CH_3COOEt = 10:1$). In the preparation of **1b**, an additional mixture of **2b** and **3b** (0.37 g, 6.38%) was isolated from the reaction mixture.

7-(2-propargyloxy)-4-methyl-2*H*-chromen-2-one (1a). Yield: 94.65%; mp: 140°C (lit.[6], 136°C); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.42 (s, 3H, 4-C**H**$_3$), 2.58–2.59 (m, 1H, -C≡C**H**), 4.77–4.78 (m, 2H, -C**H**$_2$), 6.17 (s, 1H, 3-**H**), 6.93–6.95 (m, 2H, 6 and 8-**H**), 7.53 (d, 1H, 5-**H**); MS m/z (%): 214 (M^+, 67.89).

7-(1-methyl-1-ethyl-2-propynyloxy)-4-methyl-2*H*-chromen-2-one (1b). Yield: 31.90%; mp: 110–111°C; ^{1}H-NMR ($CDCl_3$, 500 MHz δ: 1.11 (t, 3H, 1′-CH_2C**H**$_3$), 1.64 (s, 3H, 1′-C**H**$_3$), 1.90–2.04 (m, 2H, 1′-C**H**$_2CH_3$), 2.40 (s, 3H, 4-C**H**$_3$), 2.67 (s, 1H, -C≡C**H**), 6.16 (s, 1H, 3-**H**), 7.06 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.2$ Hz, 6-**H**), 7.32 (d, J = 2.2 Hz, 8-**H**), 7.49 (d, 1H, J = 8.8 Hz, 5-**H**); MS m/z (%): 256 (M^+, 6.71), 241 (M^+-CH_3, 2.04), 227 (M^+-C_2H_5, 8.38), 176 (100); Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; Found: C, 74.94; H, 6.47.

General Synthesis for 2a–b

1a–b (9.33 mmol) dissolved in 50 mL N,N-diethylaniline and refluxed for 4–7 h. Then 250 mL 7% HCl was added and extracted with ethyl

acetate (100 mL × 3). Organic layer was washed with water and brine, dried with anhydrous Na_2SO_4, and filtered. After removal of the solvent, a white solid (**2a**) was obtained by column chromatography (petroleum: $CH_3COOEt = 10:1$). With **1b** as substrate, the reaction gave the mixture of **2b** and **3b**. The recrystallization from petroleum/CH_3COOEt (10 : 1) of this mixture afforded pure **2b**.

4-methyl-2*H*-pyrano[6,5-h]2*H*-chromen-2-one (2a). Yield: 49.00%; mp: 156–158°C, (lit.[6], 156°C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.37 (s, 3H, 4-C**H**$_3$), 4.92–4.93 (m, 2H, 8-**H**), 5.83–5.89 (tt, 1H, J = 10.7 Hz, 9-**H**), 6.12 (s, 1H, 3-**H**), 6.72 (d, 1H, J = 8.7 Hz, 6-**H**), 6.98 (d, 1H, J = 10.7 Hz, 10-**H**), 7.33 (d, 1H, J = 8.7 Hz, 5-**H**); MS m/z (%): 214 (M^+, 99.69), 213 (M^+-1, 100), 186 (M^+-C=O, 26.34), 185 (M^+-1-C=O, 66.94).

4,8-dimethyl-8-ethyl-2*H*-pyrano[6,5-h]2*H*-chromen-2-one (2b). Yield: 84.75%; mp: 80–81°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.97 (t, 3H, 8-CH_2C**H**$_3$), 1.42 (s, 3H, 8-C**H**$_3$), 1.69–1.79 (m, 2H, 8-C**H**$_2$$CH_3$), 2.37 (s, 3H, 4-C**H**$_3$), 6.11 (s, 1H, 3-**H**), 5.65 (d, 1H, J = 10.2 Hz, 9-**H**), 6.95 (d, 1H, J = 10.2 Hz, 10-**H**), 6.73 (d, 1H, J = 8.7 Hz, 6-**H**), 7.33 (d, 1H, J = 8.7 Hz, 5-**H**); MS m/z (%): 256 (M^+, 3.97), 241 (M^+-CH_3, 11.12), 227 (M^+-C_2H_5, 100); Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; Found: C, 74.79; H, 6.30.

General Synthesis for 3b–d and 4b–d

A crude excessive propargylic chloride from the reaction of corresponding propargylic alcohol with thionyl chloride was added into a mixture of 4-methyl-7-hydroxycoumarin (4.00 g, 22.70 mmol), K_2CO_3 (40 g, 0.29 mol), and KI (3.77 g, 2.70 mmol) in 200 mL DMF. After stirring for 24 h at 80–90°C, the mixture was cooled, filtered, and removed from the DMF via vacuum distillation. A mixture of **2b–d** and **3b–d** was obtained with column chromatography (petroleum: $CH_3COOEt = 10:1$), which was directly used in the next reaction. The mixture of **2** and **3** in 50 mL t-butanol/H_2O (1 : 1) was added into a solution of $K_2OsO_2(OH)_4$ (16.02 mg, 0.044 mmol), $(DHQD)_2$-PHAL (34.28 mg, 0.044 mmol), $K_3Fe(CN)_6$ (2.22 g, 6.73 mmol), and K_2CO_3 (929 mg, 6.72 mmol) in 30 mL t-butanol/H_2O (1 : 1) and stirred at 0–4°C for 96–240 h. Na_2SO_3 5 g was added and extracted with ethyl acetate (50 mL × 4). Organic layer was washed with brine and dried over anhydrous Na_2SO_4. Pure **3b–d** and **4b–d** were obtained in order via column chromatography (petroleum: $CH_3COOEt = 3:1$).

4-methyl-8-(1′-methylpropyl)furano[2,3-*h*]2*H*-chromen-2-one (3b). Yield: 11.68%; mp: 82–84°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.94 (m, 3H, -CH_2CH_3), 1.35 (d, 3H, J = 6.8 Hz, 1′-CH_3), 1.65–1.70 and 1.80–1.85 (m × 2, 2H, -CH_2CH_3), 2.48 (s, 3H, 4-CH_3), 2.89–2.93 (m, 1H, 1′-**H**), 6.24 (s, 1H, 3-**H**), 6.75 (s, 1H, 9-**H**), 7.35 (d, 1H, J = 8.7 Hz, 6-**H**), 7.43 (d, 1H, J = 8.7 Hz, 5-**H**); MS m/z (%): 256 (M^+, 31.77), 241 (M^+-CH_3, 6.73), 227 (M^+-C_2H_5, 100); Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; Found: C, 74.86; H, 6.30.

4-methyl-8-(1′-methylbutyl)furano[2,3-*h*]2*H*-chromen-2-one (3c). Yield: 20.90%; mp: 84–86°C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.91–0.94 (t, 3H, -$CH_2CH_2CH_3$), 1.35 (d, 3H, J = 6.8 Hz, 1′-CH_3), 1.25–1.79 (m × 4, 4H, -$CH_2CH_2CH_3$), 2.49 (s, 3H, 4-CH_3), 2.97–3.01 (m, 1H, 1′-**H**), 6.24 (s, 1H, 3-**H**), 6.73 (s, 1H, 9-**H**), 7.36 (d, 1H, J = 8.7 Hz, 6-**H**), 7.43 (d, 1H, J = 8.7 Hz, 5-**H**); MS m/z (%): 270 (M^+, 26.72), 255 (M^+-CH_3, 2.00), 241 (M^+-C_2H_5, 7.85), 227 (M^+-C_3H_7, 100); Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71; Found: C, 75.40; H, 6.62.

4-methyl-8-(1′-ethylpropyl)furano[2,3-*h*]2*H*-chromen-2-one (3d). Yield: 65.42%; mp: 80–82°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, 6H, J = 7.5 Hz, -CH_2CH_3 × 2), 1.75 (m, 4H, -CH_2CH_3 × 2), 2.48 (s, 3H, 4-CH_3), 2.69 (m, 1H, J = 7.0 Hz, 1′-**H**), 6.24 (s, 1H, 3-**H**), 6.76 (s, 1H, 9-**H**), 7.36 (d, 1H, J = 8.7 Hz, 6-**H**), 7.43 (d, 1H, J = 8.7 Hz, 5-**H**); MS m/z (%): 270 (M^+, 34.73), 241 (M^+-C_2H_5, 100); Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71; Found: C, 75.44; H, 6.74.

(9*R*,10*R*)-9,10-dihydroxyl-8-ethyl-4,8-dimethyl-8,9,10-trihydro-2*H*-pyrano [6,5-*h*]2*H*-cheomen-2-one (4b). Yield: 46.44%; mp: 172–174°C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.01 (t, 3H, 8-CH_2CH_3), 1.42 (s, 3H, 8-CH_3), 1.70–1.79 (m, 2H, 8-CH_2CH_3), 2.40 (s, 3H, 4-CH_3), 3.23 (m, 1H, 9-O**H**), 4.00 (m, 1H, 10-O**H**), 3.95 (m, 1H, 9-**H**), 5.22 (m, 1H, 10-**H**), 6.13 (s, 1H, 3-**H**), 6.82 (d, 1H, J = 8.8 Hz, 6-**H**), 7.46 (d, 1H, J = 8.8 Hz, 5-**H**); MS m/z (%): 290 (M^+, 15.12), 205 (100), 176 (M^+-114, 18.67); Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25; Found: C, 66.07; H, 6.27.

(9*R*,10*R*)-9,10-dihydroxyl-8-propyl-4,8-dimethyl-8,9,10-trihydro-2*H*-pyrano [6,5-*h*]2*H*-cheomen-2-one (4c). Yield: 28.16%; mp: 134–136°C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.94 (t, 3H, 8-$CH_2CH_2CH_3$), 1.42 (s, 3H, 8-CH_3), 1.44–1.90 (m × 3, 4H, 8-$CH_2CH_2CH_3$), 2.40 (s, 3H, 4-CH_3), 3.24–3.30 (m, 1H, 9-O**H**), 4.06–4.20 (m, 1H, 10-O**H**), 3.91–3.95 (m, 1H, 9-**H**), 5.19–5.23 (m, 1H, 10-**H**), 6.13 (s, 1H, 3-**H**), 681 (d, 1H, J = 8.8 Hz, 6-**H**), 7.45 (d, 1H, J = 8.8 Hz, 5-**H**); MS m/z (%): 304 (M^+, 12.60), 205 (100),

176 (M^+-128, 14.23); Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62; Found: C, 66.89; H, 6.67.

(9*R*,10*R*)-9,10-dihydroxyl-8,8-diethyl-4-methyl-8,9,10-trihydro-2*H*-pyrano [6,5-*h*]2*H*-cheomen-2-one (4d). Yield: 10.68%; mp: 184–186°C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.93–0.97 (m, 6H, 8-$CH_2C\mathbf{H}_3 \times 2$), 1.62–1.68 and 1.94–2.02 (m × 2, 4H, 8-$C\mathbf{H}_2CH_3 \times 2$), 2.40 (s, 3H, 4-$C\mathbf{H}_3$), 3.12–3.13 (m, 1H, 9-O**H**), 4.15–4.16 (m, 1H, 10-O**H**), 4.06–4.08 (m, 1H, 9-**H**), 5.21–5.22 (m, 1H, 10-**H**), 6.13 (s, 1H, 3-**H**), 684 (d, 1H, J = 8.9 Hz, 6-**H**), 7.46 (d, 1H, J = 8.9 Hz, 5-**H**); MS m/z (%): 304 (M^+, 14.89), 205 (100), 176 (M^+-128, 12.77); Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62; Found: C, 66.85; H, 6.64.

ACKNOWLEDGMENT

This research was supported by a grant from National Science Foundation of China (20272010 and 30200348) awarded to P. Xia and Y. Chen, respectively.

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Received in Japan June 16, 2004